American Journal of Systems Science 2020, 7(1): 1-16
DOI: 10.5923/j.ajss.20200701.01

A Systems Thinking Perspective on Abiogenesis

Jamie P. Monat

Systems Engineering Program, Worcester Polytechnic Institute, Worcester, MA, USA

Abstract Systems Thinking involves a way of looking at the world from a holistic perspective of interactions, relationships, feedback loops, self-organization, hierarchies, and emergent properties. Abiogenesis is the theory that life on earth developed from inanimate matter. Although a lot of research has been conducted on the *elements* of abiogenesis, as yet a plausible story linking those elements together has not been developed. The purpose of this paper is to use Systems Thinking as a means for connecting the abiogenesis elements into a convincing, plausible narrative explaining how life on earth began. We start with a theory based on molecular self-organization and then use the systems thinking concepts of hierarchies, emergence, and feedback to explain the possible pathways for the evolution of life from the raw chemicals found on the primordial earth. By using a Systems Thinking lens to analyze the hierarchical structure of DNA and RNA; the characteristics of the primordial earth; the self-organizing properties of specific chemicals; the Miller-Urey and similar experiments; and the current evidence of evolution found in DNA commonalities, homologous species structures, and bacterial mutations; we are able to articulate a plausible pathway to life from inanimate chemicals. We conclude with a description of an experiment that would produce a virus-like entity from raw chemicals. The implication is that this experiment will be successfully completed within the next 10 years, convincingly demonstrating the ability of life to develop from inanimate material and thus how life on earth began.

Keywords Systems Thinking, Abiogenesis, Origin of life

1. Introduction and Background

The question of how life on earth began has intrigued humans for thousands of years. Current thinking focuses on 3 theories:

1. Divine intervention: some deity created life.
2. Panspermia: the seeds of life originated in space and developed upon reaching a suitable environment (earth).
3. Abiogenesis: life developed from the inanimate materials that were present on the Archean earth.

This paper focuses on abiogenesis and how a Systems Thinking perspective may help explain it as the likely origin of life on earth. By viewing life as a *system*, one may develop insights into its realization. Monat et al. [1] define a system as a group of interacting, interrelated, or interdependent parts that together form a unified whole, for which the arrangement of the parts is significant; that attempts to maintain stability through feedback, and that has constraints and boundaries. They further distinguish human-designed systems (which invariably were designed with some purpose in mind) vs natural systems (which may not have a specific purpose or whose purpose may be unknown to us.) Per this definition, the interacting physical and chemical constituents on the primordial earth constitute a system.

Systems Thinking has been described as a Perspective, a Language, and a Collection of Tools [2]. It suggests that one must take a holistic perspective to understand the world around us. This holistic perspective must apply not only to space, but also to time, as shown in Figure 1. In complex systems (such as the system of life) cause and effect are often widely separated in both space and time, and connecting cause and effect may require thinking very broadly, both physically and temporally.

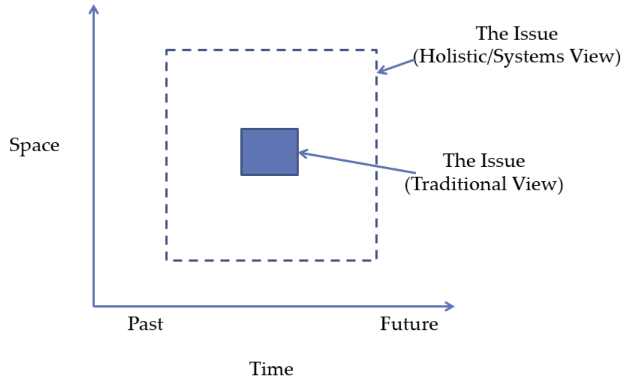


Figure 1. Holism in Both Space and Time (from [3]. Used with permission.)

Systems Thinking also teaches that in systems, relationships among components are often more important

* Corresponding author:
jmonat@wpi.edu (Jamie P. Monat)
Received: Nov. 23, 2020; Accepted: Dec. 21, 2020; Published: Dec. 28, 2020
Published online at http://journal.sapub.org/ajss

than the components themselves. Furthermore, those relationships often result in *feedback loops*: both reinforcing and stabilizing. These systemic relationships result in *emergent* system properties: properties of the system that emerge because of the relationships among components and that typically would not be predictable from the properties of the individual system components. Examples are the V-formations of geese, the schooling of fish, ripples on sand dunes, zebra stripes, the spiral patterns of galaxies, the pattern of a nautilus's shell, the spiral patterns observable in pine cones and pineapples, and the repeating patterns of nucleotides (linked assemblies of phosphate groups, ribose, and a base) in DNA. Life itself may be a systemic emergent property. Systems Thinking further argues that system components often *self-organize* into hierarchical structures and that most stable systems are hierarchical in nature. Camazine [4] states that "Self-organization is a process in which an emergent pattern at the global level of a system emerges solely from numerous interactions among the lower-level system components. Moreover, the rules specifying interactions among the system's components are executed using only local information, without reference to the global pattern. In other words, the pattern is an emergent property of the system, rather than a property imposed on the system by an external influence." Self-Organization is the *process* by which systems develop emergent patterns. These elements of systems thinking: holism, relationships, feedback loops, hierarchies, emergent patterns, and self-organization---are helpful in supporting abiogenesis as the basis for life on earth.

It is important to identify the *underlying forces* that yield self-organization and hence, emergent patterns. In human-designed systems, those underlying forces are usually mental models. In natural systems, the underlying forces are physical (such as gravity, electromagnetic forces, nuclear forces), chemical (such as hydrogen bonding, Vander Waals forces, hydrophilicity and hydrophobicity), and biological (such as genetic and instinctive forces.) The instinctive forces in animals correspond to the mental models in human-designed systems. The underlying systemic chemical forces are especially relevant to the current study of abiogenesis with respect to molecular self-organization.

Molecular self-organization (also known as molecular self-assembly) is quite common. In a super-saturated sugar solution, highly ordered crystals will automatically form and grow on a nucleation site. The same is true for silicon dioxide (quartz), sodium chloride (salt) and many other crystals. The forces underlying molecular self-organization include + and – electric charges, hydrophilicity/hydrophobicity, the physical molecular shapes ("lock and key" mechanisms), and Van Der Waals forces such as hydrogen bonding. Interestingly, molecular self-organization can yield a *self-replicating chemical system*.

A blueprint for a minimally self-replicating system is shown in Figure 2.

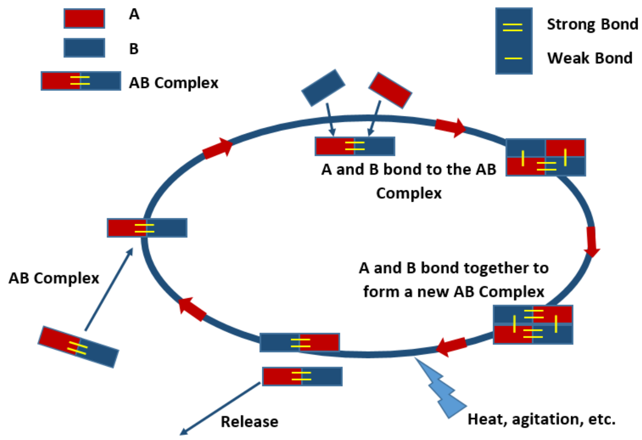
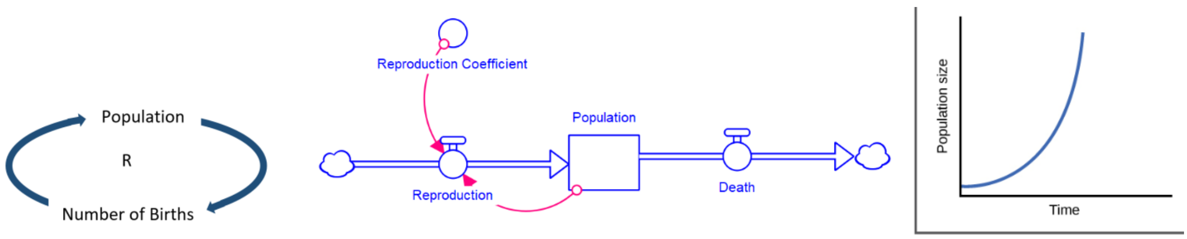


Figure 2. Blueprint for a Minimal Self-Replicating System

In Figure 2, 3 species are shown: Species A, Species B, and the AB Complex consisting of A and B bound together. In this scenario, A and B must be able to bond both strongly (perhaps by ionic bonds) and weakly (perhaps by hydrogen bonds). The AB Complex replicates itself by first attracting individual A and B species that are available in the surrounding medium and binding them weakly to its surface. Because of their newfound proximity, A and B then bond together strongly, forming a new AB Complex which is the complement of the original AB complex. The new AB Complex is released from the original AB complex by external forces (perhaps simple agitation, UV radiation, or thermal energy.) Now both the original and replicant AB Complexes are free to replicate again. Systems Thinkers recognize this as a reinforcing feedback loop that typically leads to exponential growth of the AB Complex; this reinforcing feedback loop is the basis for exponential population growth as shown in Figure 3, which also shows a stock-and-flow diagram and the corresponding Behavior-Over-Time (BOT) plot.



(a) (b) (c)

Figure 3. Population Growth: (a) Causal Loop Diagram (b) Stock-and-Flow Diagram (c) Population Behavior-Over-Time

Self-replicating molecular systems do exist. Rotaxane is a dumbbell-shaped molecule that is threaded through another molecule in a wheel-and-axle structure. Douglas Philp and his colleagues from the University of St. Andrews [5] have developed a form of rotaxane that can self-replicate—that is, it can make copies of itself. Fulvene is a cyclic organic compound whose self-replication has been demonstrated by Dieckmann et al. [6]. Self-replicating chemical systems are also discussed by Liu and Sumpter [7], Liu et al. [8], Clixby and Twyman [9], and many others. Liu at al. [8] have described the Spontaneous Emergence of Self-Replicating Molecules Containing Nucleobases and Amino Acids, which is especially relevant. In their study, they demonstrated that amino acids and nucleobases can be made to replicate spontaneously under certain conditions.

In the early 1970s, Manfred Eigen and Peter Schuster conceptualized the “hypercycle,” a cycle of connected, self-replicating macromolecules [10]. In this cycle, several molecules are linked together in a reinforcing feedback loop, with each molecule facilitating the creation of its successor (Figure 4) and the final molecule catalyzing the first.

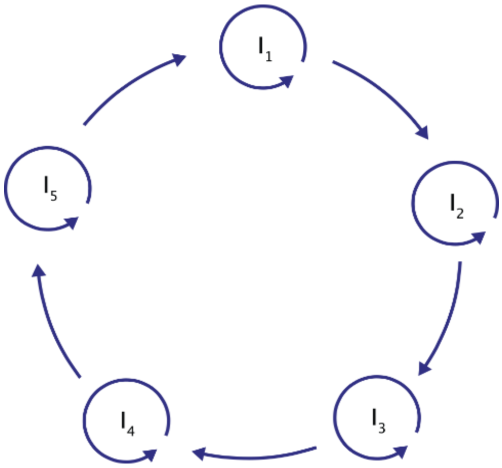


Figure 4. The Eigen-Schuster Hypercycle by Szostak [10] is licensed under CC BY-SA 4.0

Szostak et al. [10] have shown mathematically how, in a simulated stressed environment, hypercycles can result in the evolution of their constituents to new species. This theoretical approach was supported by discovery in 2012 of ribozymes (RNA molecules that act as enzymes) capable of catalyzing their own chemical reactions [11].

Once an inanimate chemical system can self-replicate, in a stressed environment it can evolve to achieve better fitness and greater complexity in the process of *chemical evolution* [12,13]. It is possible that the self-replication of chemical species on the primordial earth eventually led to life.

A possible mechanism for such a development (based upon feedback) is depicted in Figure 5. In this Darwinian mechanism, the conventional population growth mechanism depicted in Figure 3 is modified to include environmental stress and mutations. In the figure, classical exponential population growth mechanics are applied to self-replicating chemical species. In a stressed environment (as would be found on the primordial earth) as the population of a chemical species grows exponentially (due to self-replication) and is subject to random mutations, species that develop poorer fitness die off while species that develop better fitness survive and procreate. Typically better fitness = greater complexity as the newer species has more mechanisms to deal with environmental stress [14] and therefore displays both greater longevity and more efficient reproduction capability. New et al. [15] describe this non-genomic evolution of prebiotic chemicals as an “inherited efficiencies model” and Monaco and Montozon [13] have modelled this mathematically.

Complexity can be defined in many ways. A Systems thinking definition argues that systems (including chemical systems) display “Organized Complexity” comprising feedback loops, self-organization, emergence, and interdependencies [16]. Complex Organized systems are distinguished from simple and disorganized structures in Figure 6.

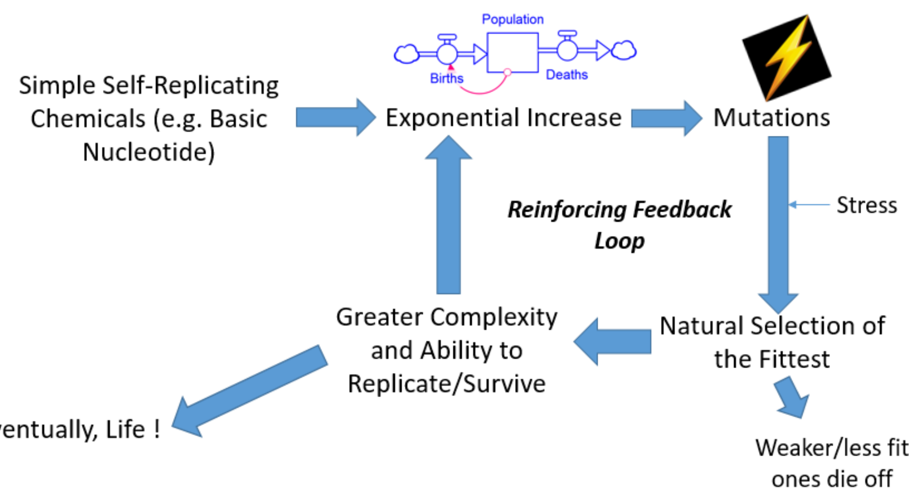


Figure 5. Reinforcing Feedback Loop Yielding Increased Complexity

	Simple	Complex
Organized (Show Structure)	Crystals, Simple Machines	Display hierarchies, feedback loops, interdependencies, self-organization, emergence: Biological systems, ant colonies, cities, economic systems, chemical systems, the human body
Disorganized (Random)	Bowl of fruit, Tools in a Toolbox	Many elements; chaotic: Gas Molecules, Sand on the Beach

Systems

Figure 6. Organized Complexity

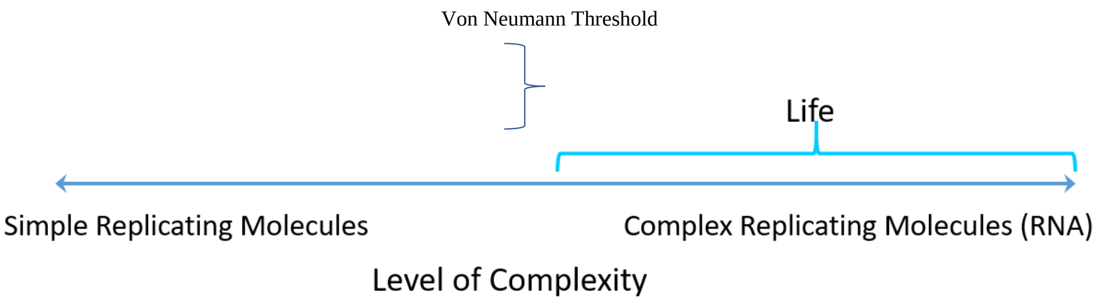


Figure 7. Life as a Function of Complexity

Although "life" is not well-defined, it is generally accepted that living things are more complex than non-living things [17,18]. Complexity occurs on a continuum, some fuzzy threshold (the "von Neumann threshold of complexity" [19]) beyond which we define as "living" (Figure 7.)

It is also widely agreed that for an entity to be defined as "alive" it must *at least* be able to self-replicate and to evolve (see for example [13].)

In his book, *A Short History of Nearly Everything* [20] Bill Bryson states, "Chemical reactions of the sort associated with life are actually…commonplace. Lots of molecules in nature get together to form long chains called polymers. Sugars constantly assemble to form starches. Crystals can do a number of lifelike things---replicate, respond to environmental stimuli, take on a patterned complexity. They've never achieved life itself, of course, but they demonstrate repeatedly that complexity is a natural, spontaneous, entirely commonplace event. There may or may not be a great deal of life in the universe at large, but there is no shortage of ordered self-assembly, in everything from the transfixing symmetry of snowflakes to the comely rings of Saturn." Bryson supports the views that "life" is associated with increased complexity and that self-organization is common throughout the universe.

Thus, there is substantial evidence demonstrating the ability of inanimate chemicals to self-organize into self-replicating systems and for those chemical systems to evolve into species with greater complexity and greater fitness.

2. Theory and Supportive Evidence

A great deal of research has been devoted to the *elements* of abiogenesis. A Systems Thinking perspective, however, would study the problem holistically. It would recognize the inter-connectedness of the raw materials on the primitive earth with each other and with the environment. It would recognize that the system of life evolved step-wise over time and hierarchically as complexity increased. It would attempt to identify the self-organizational processes they yielded emergent patterns in the macroscale (the repeated evolution of new life forms) and in the microscale (the repeated nucleotides in a DNA molecule) and attempt to identify the causal relational feedback loops that yielded them. It would try to understand the underlying forces that yielded the self-organization and self-assembly of the components of life. Importantly, it would integrate the research that has been conducted on the fundamental elements of abiogenesis and integrate it into a plausible story. And it would identify systemic gaps in our knowledge and perhaps offer guidance in addressing those gaps.

The Systems Thinking perspective would argue that the evolution of life from inanimate chemicals in the primordial ooze would necessarily have proceeded step-wise and hierarchically, as more complex structures evolved from less complex ones. A block diagram of a proposed pathway to life is shown in Figure 8.

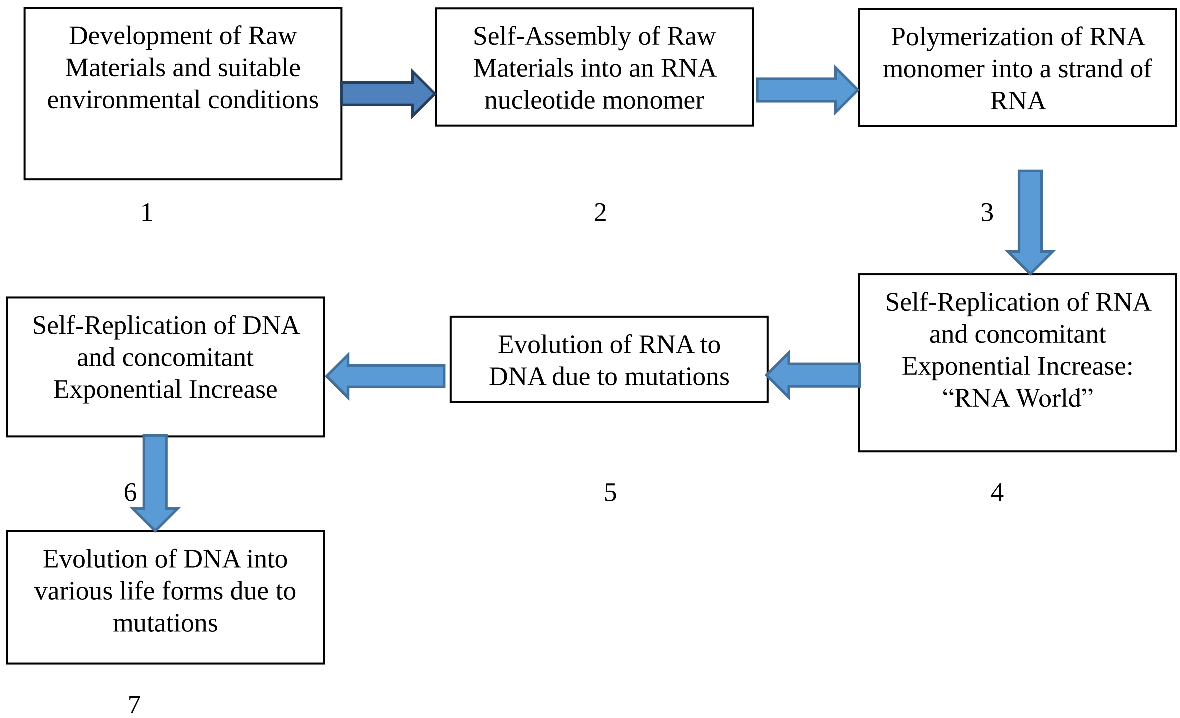


Figure 8. Hypothetical Pathway to Life from Raw Materials

Note that each of the 7 steps can be defined as a system unto itself. Each step of the process is discussed below.

3. The Structure of DNA and RNA

DNA and RNA (depicted in Figure 9) both comprise carbon, hydrogen, oxygen, phosphorus, and nitrogen. The 2 molecules are very similar, except that DNA is a double helix while RNA is a single helix. Additionally, DNA is composed of the 4 nucleobases cytosine, guanine, adenine, and thymine while in RNA uracil is substituted for thymine. A final difference is that the ribose in RNA is replaced by deoxyribose in DNA.

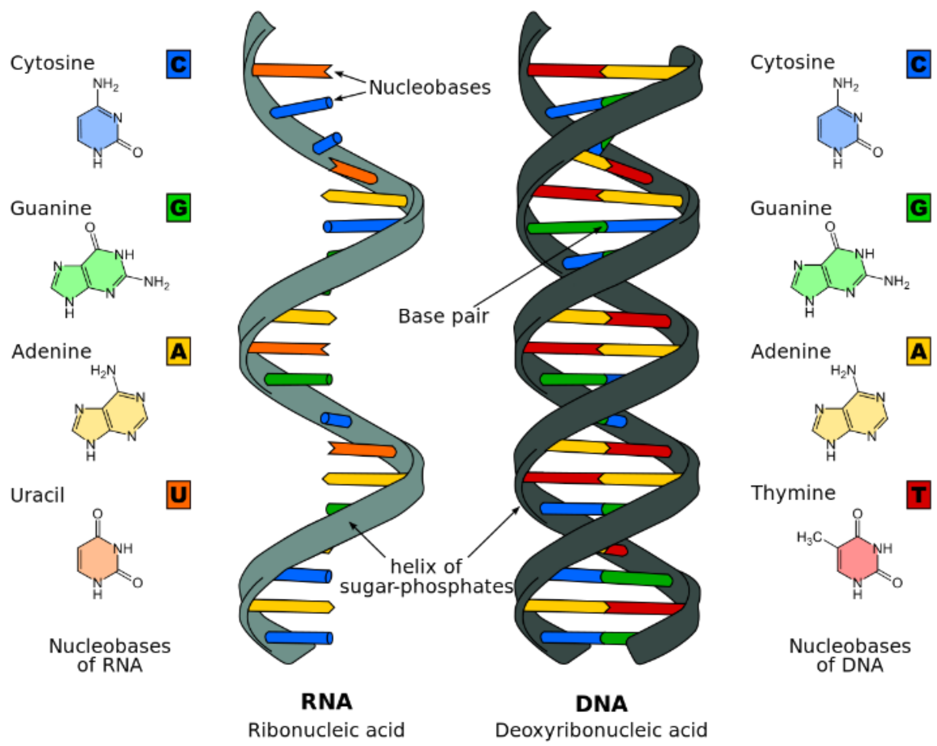


Figure 9. RNA and DNA. “Difference DNA RNA-EN.svg” by Sponk (Wikimedia Commons) is licensed under CC BY-SA 3.0

Conventional wisdom is that RNA preceded DNA in “RNA world” and that DNA subsequently evolved from RNA [21]. RNA is a somewhat fragile molecule and is easily damaged by enzymes; DNA displays better fitness because the double helix results in a more stable molecule.

Figure 10a is a schematic of the well-known DNA double helix. Figure 10b shows the helix untwisted, clarifying that there are 2 sugar-phosphate backbones linked together by many nitrogenous base pairs. Figure 10c shows the same untwisted helix at the molecular level, identifying the atomic structure. Note the *emergent pattern* of repeating nucleotides. Figure 10c shows that DNA is an extremely complex molecule, with over 200 billion atoms. The probability that, in the Archean sea, atoms of C, H, O, P, and N came together in just the right way to form a DNA (or RNA) molecule, by chance, is infinitely small: Sir Fred Hoyle [23] claims that it is less than 1 in $10^{40,000}$. In nature, it is rare for things to develop spontaneously from high-entropic (disorganized) to low-entropic (highly organized) forms; it is much more common (and logical, from an energy perspective) for them to develop step-wise, or hierarchically.

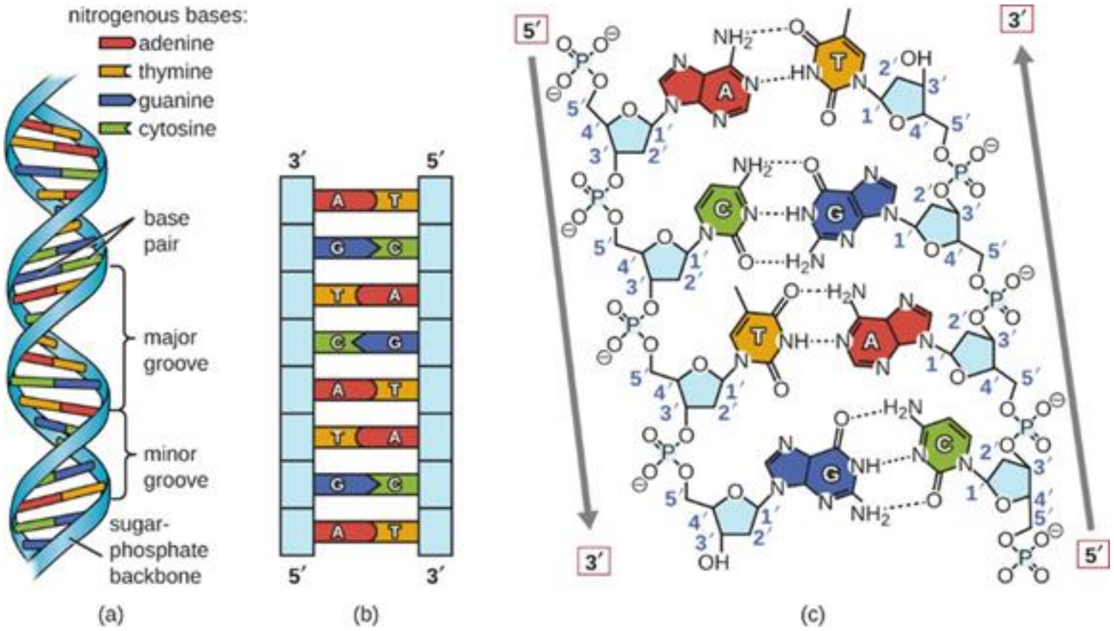


Figure 10. The Double Helix Model of DNA [22] is licensed under CC BY-SA 4.0

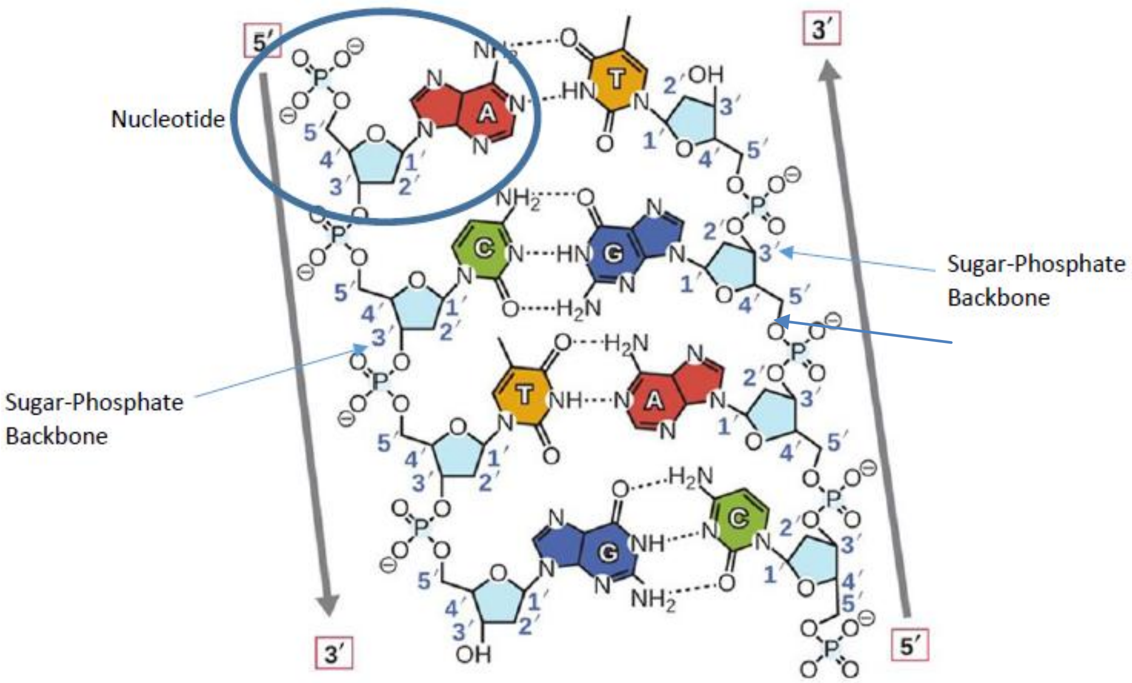


Figure 11. Repeating Nucleotide comprising a Phosphate group, a ribose group, and a base (DNA is shown; structure is similar for RNA but with only 1 sugar-phosphate backbone) (The Double Helix Model of DNA [22] is licensed under CC BY-SA 4.0)

Complex, self-organized systems are often hierarchical because of the stability and efficiency afforded by hierarchies. Dana Meadows [24] states that “Complex systems can evolve from simple systems only if there are stable intermediate forms. The resulting complex forms will naturally be hierarchic. That may explain why hierarchies are so common in the systems nature presents to us. Among all possible complex forms, hierarchies are the only ones that have had the time to evolve.” The unstable forms die off. Hierarchies thus facilitate the evolution of simple systems into complex systems. A good example is endosymbiosis: the modern eukaryotic plant cell is a hierarchy of substructures, including photosynthesizing chloroplasts and energy-producing mitochondria, which are fairly complex structures themselves. It is believed that the chloroplasts and mitochondria were originally independent organisms that were engulfed by a primitive cell. The 3 structures were symbiotic, and a substantially more complex, stable cell was formed: one that had better fitness because of its new-found ability to manufacture its own food and energy. Systems tend to become more complex, with greater hierarchical structure, as they evolve.

Applying Systems Thinking to the structure of both RNA and DNA, one may recognize that each is a *system:* they each comprise many components, the relationships (balancing and reinforcing feedback loops) among which dominate system behavior. They display self-organization and emergent properties. They interact with their environment. They exhibit organized complexity in the form of hierarchies, comprising repeating nucleotides of ribose, phosphate, and a base (see Figure 11.)

These 3 sub-units are depicted separately in Figure 12; they are quite simple and comprise only a few atoms each.

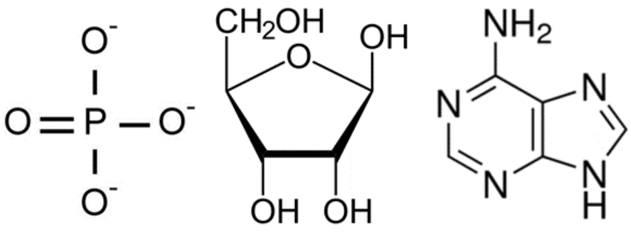


Figure 12. DNA Sub-Units

The question may now be posed, “What is the probability that, in the Archean sea, atoms of C, H, O, P, and N came together in just the right way to form these 3 sub-units, which *then* combined to form RNA, and subsequently DNA?” The probability is much higher than the probability of the raw atoms spontaneously combining to form RNA. The probability may be high enough to actually yield an RNA molecule.

Step 1: Development of Raw Materials and suitable environmental conditions

Consider the primitive earth, 4 billion years ago (Figure 13).

Figure 13. Artist’s Rendition of the Primitive Earth (Theia Impact on Early Earth, by Bill Carr. bcarr@comcast.net, https://www.artstation.com/billcarr. Used with permission)

Carbon dioxide, water vapor, methane, sulfur dioxide, ammonia, hydrogen cyanide, and other gases are abundant as the result of volcanos, meteorites, comets, and other natural phenomena. Water is abundant in the seas and in the atmosphere. The temperature is warm [25] and there are electric discharges due to lightning and ultraviolet radiation from the sun. There are plenty of raw materials and sources of energy. Solid surfaces such as clays and solid-liquid interfaces abound. Cycles of night and day, seasons, precipitation, and weather/climate patterns result in oscillations of temperature, moisture, and pH.

Step 2: Self-Assembly of Raw Materials into an RNA nucleotide monomer

In 1953 Stanley Miller and Harold Urey conducted an experiment to see if complex organic compounds would self-assemble under the conditions present on the primordial earth. Their apparatus is shown in Figure 14. Miller and Urey heated saline solution (representative of the earth’s primordial oceans) in a flask. The vapors from the flask were mixed with gaseous hydrogen, ammonia, and methane, all of which were believed to exist in the primordial atmosphere as a result of volcanic eruptions. This simulation of the primitive earth atmosphere was then subjected to electric discharges (simulating lightning) for a week. (Presumably lightning broke the chemical bonds of the stable gaseous molecules to yield free radicals that could then recombine to form new molecules.) At the end of the week, vapors from the simulated atmosphere were condensed and analyzed. The researchers found many complex organic molecules, including several amino acids (the building blocks of protein.)

In 1961, Juan Oro repeated a version of the Miller-Urey experiment, this time using ammonia, hydrogen cyanide, and water vapor as the introduced gases [26]. Oro found significant quantities of the nitrogenous base adenine in the condensate.

Earlier (in 1951) Bernal had hypothesized that clay minerals might have facilitated abiogenesis because of their abilities to catalyze organic reactions as well as to concentrate and protect species against radiation [27]. Following this lead, Shimoyama et al. [28] also repeated the Miller-Urey experiment but added montmorillonite clay to the mixture. They found that the yield of amino acids increased substantially. In 1989 Yuasa conducted a similar experiment sparking mixtures of HCN and NH_4OH in the presence of montmorillonite clay [29]. He obtained the amino acids glycine, alanine, and aspartic acid. Many more experiments have demonstrated the catalytic and selective properties of clays [30]. These experiments demonstrate the importance of considering the impact of the system environment on system performance. There are likely additional environmental factors that facilitated abiogenesis.

In 2014, Miller and Urey's experiment was repeated by Keller, Turchyn, and Ralser, but this time adding ferrous iron (Fe^{++}) which was also present on the primordial earth, to the mix [31]. In this experiment, the researchers discovered both phosphate and ribose in the condensate. Thus, Miller & Urey; Oro; and Keller, Turchyn, and Ralser demonstrated that the building blocks of both proteins (amino acids) and DNA (Phosphate, ribose, nitrogenous base) could develop spontaneously under the conditions present on the primordial earth. The final step: the self-assembly of a phosphate group, ribose, and a base into a nucleotide has not yet been demonstrated to any significant degree. A possible mechanism for this hierarchical synthesis is shown in Figure 15.

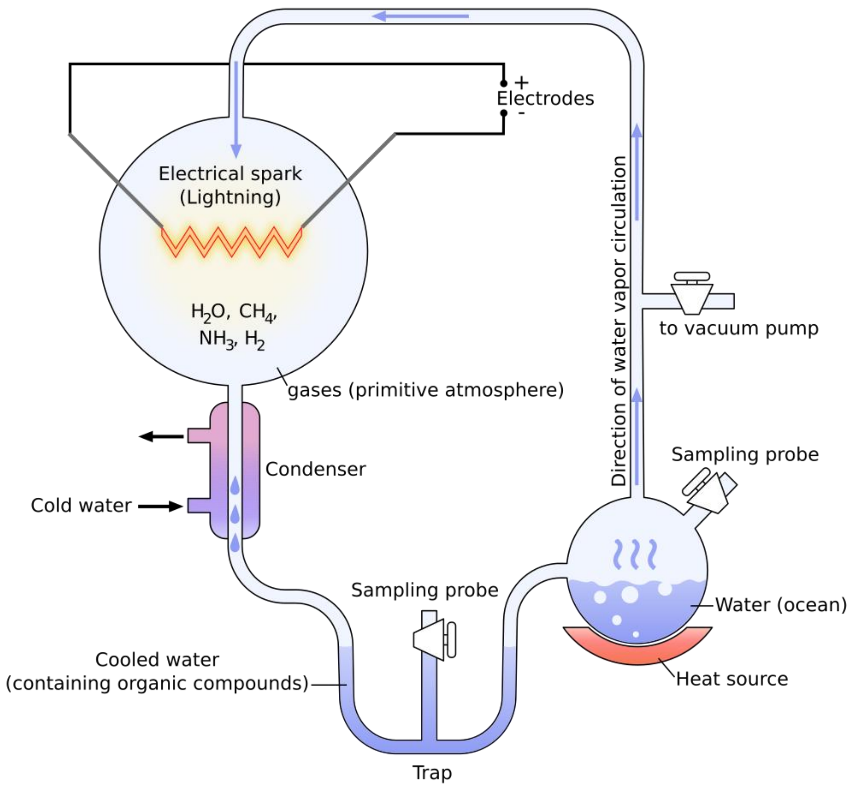


Figure 14. The Miller-Urey Experiment by Wikimedia Commons is licensed under CC BY-SA 3.0

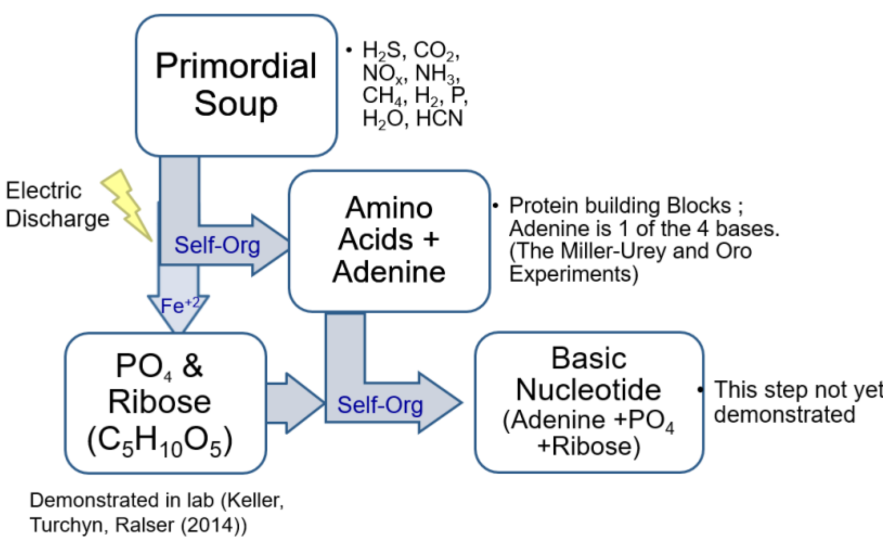


Figure 15. Possible Abiogenesis Mechanism Based on Miller-Urey Experiment

In this mechanism, amino acids and the 4 nitrogenous bases form spontaneously from the primitive atmosphere under the presence of lightning. Where ferrous iron is present, phosphate and ribose molecules also form spontaneously. The 3 sub-units phosphate, ribose, and a base then join to form a nucleotide. Once one nucleotide has formed, additional nucleotides link to it due to molecular self-organization (probably covalent bonding) in a reinforcing feedback loop [32]. Eventually, a chain of nucleotides develops and there exists a precursor to RNA. This RNA precursor likely evolved over time to become our current version of DNA.

Unfortunately, the final synthesis step of Figure 15 has not been observed. Specifically, ribose refuses to bond to a base due to both kinetics and thermodynamics [33,34]. However, Nicholas Hud and his team at the Georgia Institute of Technology have demonstrated an alternate self-assembly pathway for ribose-base bonding that may obviate this obstacle [35,36]. They added triaminopyrimidine (TAP) to ribose and, taking a broader systems thinking perspective, subjected the mixture to conditions intended to mimic a drying pond on the primordial earth. They observed significant bonding between the ribose and the TAP and concomitant high yields of bonded ribose-TAP molecules, which they name "TARC," thus overcoming the inability of ribose and a nucleotide to bond as hypothesized in Figure 15. There are 2 problems with this theory, however: 1) although the resulting TARC consists of ribose bonded to a base, the base is similar to but not exactly the same as one of the canonical bases found in DNA or RNA, and 2) on the primitive earth, where did the triaminopyrimidine come from? Thomas Carell has demonstrated the self-assembly of formamidopyrimidines (similar to triaminopyrimidine) from raw components on the early earth [37] so that may explain this issue. Study co-author Brian Cafferty remarked, "It is amazing that these nucleosides and bases actually assemble on their own, as life today requires complex enzymes to bring together RNA building blocks and to spatially order them prior to polymerization."

But the pathway shown in Figure 15 is not the only route to the creation of DNA. Matthew Powner's team [33,38] have demonstrated an alternate hierarchical pathway to the formation of RNA, also deriving from the assembly of simple sub-units (Figure 16).

In Powner's mechanism, the synthesis starts with 5 simple sub-units, all of which are believed to have been present on the primitive earth: phosphate, cyanimide, glycoaldehyde, glyceraldehyde, and cyanoacetylene (although these names sound intimidating, the molecules that they represent are quite simple.) Keller, Turchyn, and Ralser [31] previously demonstrated the self-assembly of phosphate from pre-biotic molecules. In an experiment similar to that of Miller and Urey, Sanchez et al. [39] found cyanoacetylene in the reaction products of a methane-nitrogen mixture that had been subjected to electric discharges. The other 3 sub-units required for Powner's mechanism: cyanimide, glycoaldehyde, and glycerolaldehyde, have not yet been shown to self-assemble in the lab, but in 2006, Thaddeus [40] noted the detection of heavier organic molecules like cyanamide, glycolaldehyde, and glycerolaldehyde in interstellar gas. (This rationale for the presence of these 3 organic compounds on the primitive earth does not seem convincing. Simply because they were present in interstellar gas does not mean that they were present in sufficient concentrations on the surface of the primitive earth. Demonstrating the self-assembly of these compounds from the raw materials that were thought to be present is a topic for research. This thus represents a weakness in Powner's proposed mechanism.) Thus the 5 building blocks *may* have been present on the primitive earth. Powner demonstrated that in the presence of UV light and phosphate (which acts as a pH and chemical buffer) cyanimide and glycoaldehyde combine to form 2-aminooxazole which then combines with glyceraldehyde to yield pentase amino-oxazoline (PAO.) The PAO then combines with cyanoacetylene to form anhydroarabino nucleoside which then combines with a phosphate group to form β-ribocytidne, one of the DNA nucleotides. As noted, most of Powner's mechanism (with the exception of the initial self-assembly of cyanamide, glycolaldehyde, and glycerolaldehyde) has been demonstrated in the lab.

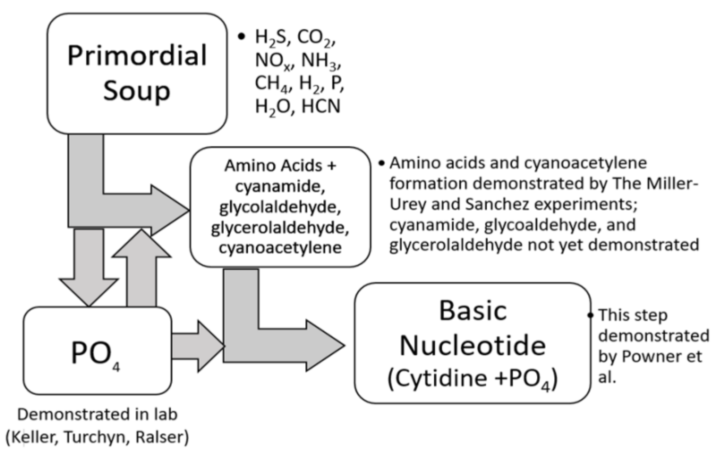


Figure 16. The Powner Mechanism of RNA Formation

Still another pathway (FaPy) has been proposed by Professor Thomas Carell and his team at the Ludwig Maximilian University of Munich [37]. Carell's team have demonstrated that if a mixture of formic acid, acetic acid, sodium nitrite, nickel, iron, and a few nitrogenous compounds (all of which have been shown to have been present or self-assembled from raw materials on the primordial earth) are subjected to alternating cycles of pH, temperature, and moisture, then formamidopyrimidines will self-assemble and will subsequently develop into several of the nitrogenous bases (adenosine and guanosine.) The bases would then combine with ribose and phosphate to form an RNA nucleotide. The beauty of Carell's pathway is that it adopts a Systems Thinking perspective wherein the system chemical components interact with each other *and with the environment*: periodically active hot springs, geothermal activity, and weather or climate variations could have provided the alternating conditions required for this process. Carell's pathway is depicted in Figure 17.

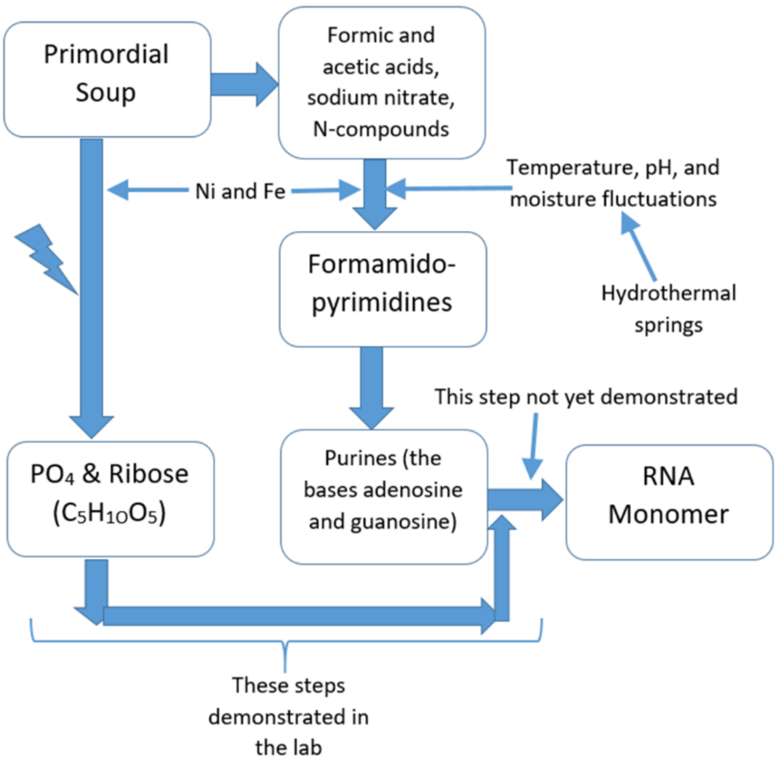


Figure 17. The FaPy Pathway per Carell

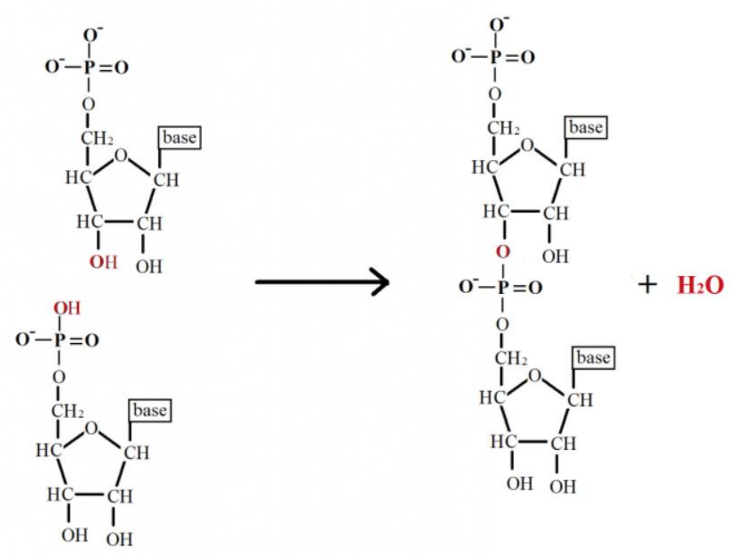


Figure 18. RNA Polymerization by Phosphate Bonding ("Phosphodiester Bond" by School of Biomedical Sciences Wiki is licensed under CC BY-SA 3.0)

It would be interesting if Carrell's approach were to be combined with Hud's ribose-base co-condensation approach in that Carrell demonstrates the auto-formation of pyrimidines while Hud demonstrates their self-assembly with ribose.

The point is that whichever pathway is correct, all models incorporate interactions among the systemic components and their environment, **hierarchical** self-organization (due to naturally-occurring underlying chemical and physical forces) of aldehydes, amino acids, and other organic molecules from simple molecules, and the subsequent self-assembly of those more complex molecules into nucleotides which then self-assemble to form RNA and eventually DNA.

Step 3: Polymerization of RNA monomer into a strand of RNA

Once an RNA nucleotide has formed, it is still not RNA until many nucleotides polymerize into a helix. Todisco [32] has described how short segments of RNA nucleotides *self-assemble* to form 100-unit –long chains. In this marvelous set of experiments involving Systems Thinking concepts, Todisco showed that under conditions of molecular crowding, RNA oligomers can self-assemble into linear *liquid crystals* (which are substances that flow like liquids but whose molecules have a fixed, crystal-like orientation.) The liquid crystals form physical templates: long, columnar structures that guide the addition and orientation of additional nucleotides, preventing intramolecular bonding to form interfering cyclic structures, but instead extending the chain length by bonding the ribose units, end-to-end, with phosphate groups (see Figure 18.) The longer these chains get, the more they force available free nucleotides into a consistent linear geometry, thus extending the polymer chain length in a reinforcing feedback loop (Figure 19.) Thus, this process involves the Systems Thinking steps of self-organization, reinforcing feedback loops, and systemic hierarchies.

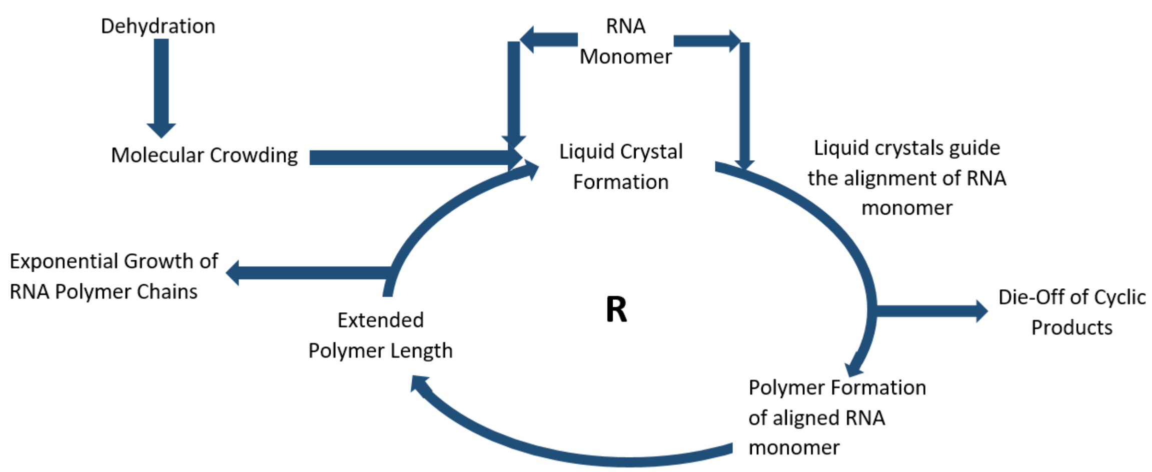


Figure 19. Reinforcing Feedback Loop of Liquid Crystal and Polymer Formation

Todisco posits that DNA polymerization may occur via a similar vehicle. This approach contrasts with those based on enzymatic reactions to polymerize RNA nucleotides. In those approaches, RNA displays self-catalytic properties in that it can catalyze its own reactions in a reinforcing feedback loop.

Step 4: Self-Replication of RNA and concomitant Exponential Increase: "RNA World"

It has been experimentally demonstrated that RNA can self-replicate [41,42]. This self-replication occurs at low temperatures (42℃) and without proteins or other biologic materials required. It leads to an exponential increase in the population of RNA molecules, as depicted schematically in Figure 20 for general populations, with a doubling time of ~5 minutes. This self-replication thus provides the opportunity for RNA to evolve to better fitness. Here again we see the Systems Thinking construct of a self-organized reinforcing feedback loop leading to exponential growth.

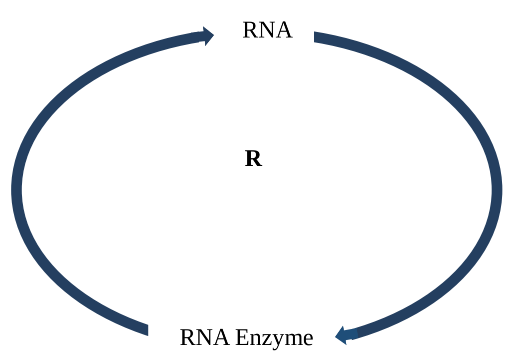


Figure 20. RNA Self-Catalysis

Step 5: Evolution of RNA to DNA due to mutations

The evolution of RNA into DNA seems plausible. As noted in Figure 5 above, populations evolve into news species under conditions of stress and mutations, resulting in increased populations of species with greater fitness and reduced populations of species with poorer fitness. As noted above, DNA is more fit than RNA because it is more stable (and less subject to enzymatic degradation) and also because it reproduces faster than RNA. Additionally, the building blocks of DNA are almost identical to those of RNA, so it is probable that DNA building blocks were present in an environment that already contained RNA. Cojocaru and Unrau [43] of Simon Fraser University discuss several possible mechanisms for the evolution of RNA to DNA, as do Lazcano et al. [44] but as yet, there is no strong experimental proof of one of these.

Step 6: Self-Replication of DNA and concomitant Exponential Increase

The self-replicating ability of DNA has been repeatedly demonstrated and is well-understood [45]. DNA replication occurs in 3 steps: 1) the separation of the 2 DNA strands, which is initiated by the protein helicase 2) the priming of one of those strands by the protein primase, and 3) the assembly of the new complimentary strand by the protein polymerase (Figure 21.) DNA replication is a symphony of *reinforcing and stabilizing feedback loops.* First, there is the overall reinforcing feedback loop describing self-replication, as shown in Figure 5. In addition, there are many (perhaps dozens) of additional feedback loops responsible for the initiation of the DNA unwinding and unzipping, the activation and deactivation of the proteins that control replication, and the checkpoints throughout the process that ensure complete and accurate transcription [46,47,48].

DNA replication has been demonstrated in the lab via a Polymerase Chain Reaction [49] and is often used forensically to identify criminals. Cyclic heating and cooling cause the double helix to separate and then replicate. Using these methods, researchers have been able to generate significant quantities of DNA from very small initial samples. There is little doubt that once DNA materialized on the primordial earth it was capable of self-replication under the existing conditions.

DNA replication is a phenomenal example of systemic feedback control and chemical self-organization due solely to underlying chemical and physical forces. Note that in the mechanism described, proteins are required as functional adjuncts—this subject will be addressed shortly.

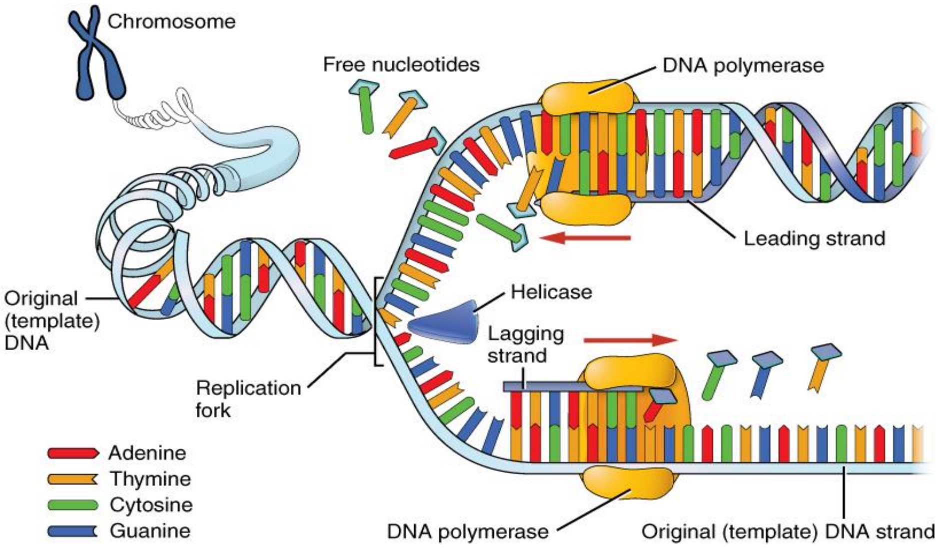


Figure 21. DNA Replication by OpenStax Anatomy and Physiology (Wikimedia) is licensed under CC BY 4.0

Step 7: Evolution of DNA into various life forms due to mutations

Once DNA was formed and was capable of self-replication, it was free to mutate and evolve into various forms of life. Moelling et al. [50] and others hypothesize that the first life forms were virus pre-cursors called ribozymes. Ribozymes are RNA molecules with catalytic capabilities, capable of replication, cleaving, joining, and forming peptide bonds. They can chemically self-replicate [41] and have been shown to mutate and evolve. Ribozymes share many of their characteristics with viruses, the simplest of which are basically strands of DNA or RNA encased in a protein capsule.

Viruses reproduce quickly and have relatively high mutation rates, which allows them to adapt quickly to changing environments. (This is why catching the common cold does not impart immunity and why we must be re-inoculated against the influenza virus each year.) It is thus highly probably that once viruses materialized, they evolved into many more advanced life forms.

There is much evidence, both direct and indirect, to support biotic evolution due to DNA or RNA mutations. First, there is substantial evidence in the form of homologous structures in various animals (such as the similarities in the leg bones of humans, apes, horses, dogs, whales, and mice.) Second, if one examines the development after fertilization of many different species, one sees that early in their embryonic development, various different animals look surprisingly similar. Third, much human DNA is shared by various animals: 98% of our DNA is shared with chimpanzees, 92% with mice, 44% with fruit flies, 26% with yeast, and even 18% with plants. The most compelling evidence, however, is the current and ongoing evolution of bacteria to antibiotic-resistant strains and the evolution of the flu virus to new forms in response to the stressed environments that they encounter [51] Using a molecular clock technique, Tamura et al. [52] have actually measured the rate of fruit fly (Drosophila melanogaster) evolution as 11.1 mutations per kilobase pair per million years. They were able to correlate significant evolutionary changes in fruit fly DNA with major climatological changes during the Cenozoic era, suggesting that the evolutionary changes were a response (increased fitness) to the stress of a changed environment.

4. The Role of Proteins

It is widely believed that both DNA and proteins were required for life to begin on earth: DNA carries the information while the proteins execute the instructions. Proteins facilitate the formation of DNA via their enzymatic activity unzipping, priming, and polymerizing new strands of RNA, and RNA directs the production of proteins by using sequences of 3 RNA bases to signal which amino acids to form [53] (see the reinforcing feedback loop depicted in figure 22.) So it appears that in order to materialize, DNA and proteins each require the other.

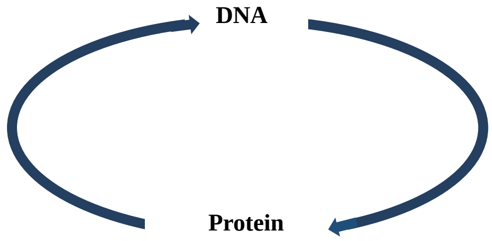


Figure 22. Causal Loop Diagram showing the Reinforcement of Proteins and DNA

But this raises additional questions as the DNA-replicating proteins (helicase, primase, and polymerase) are themselves complex molecules that would have had to self-assemble, and protein assembly is mediated by DNA. So we have a chicken-and-egg issue. Some think that DNA materialized first, others think that proteins developed first, and still others believe that they both appeared simultaneously. However, Deamer [54] suggests an alternate pathway to protein formation that does not require either DNA or RNA. In this pathway, the simple amino acids found in Miller and Urey's experiment could have linked together by virtue of the heating and drying cycles that were present near prebiotic geothermal sites. Fox and Harada [55] showed that simple heating of amino acids produced amino acid polymers much like proteins. Rohlfing [56] demonstrated similar results at lower temperatures. In 2004, Leman showed that carbonyl sulfide (a typical component of volcanic gases) promotes amino acid polymerization into proteins without the need for thermal cycling [57]. These mechanisms obviate the chicken-and-egg question surrounding DNA and proteins in that each could have evolved independently.

5. Conclusions and Future Work

Systems Thinking may help to understand how life developed on earth. Its principles of feedback loops, hierarchies, and self-organization may explain how the first RNA sub-units (phosphate groups, ribose, and nitrogenous bases) individually self-assembled on the primordial earth and then assembled to form a DNA precursor. Life on earth may have originated *hierarchically* due to molecular self-organization (involving *feedback loops*) which, in turn, occurred because of the underlying forces of hydrogen bonding, electrostatic forces, Vander Waals forces, etc.

Of the 7 steps denoted in Figure 8, 5 (steps 1, 3, 4, 6, and 7) have already been demonstrated either in the laboratory or *in situ*. The 2 steps that have not been proven conclusively are:

Step 2: Self-Assembly of Raw Materials into an RNA nucleotide monomer

- The self-organization of phosphate, ribose, and a base into a basic nucleotide.
- In Powner's mechanism, the self-organization of cyanamide, glycolaldehyde, and glycerolaldehyde from raw materials thought to have been present on the surface of the primordial earth.
- In Hud's model, although the resulting TARC consists of ribose bonded to a base, the base is similar to but not exactly the same as one of the canonical bases found in DNA or RNA.
- In Hud's model, on the primitive earth, where did the triaminopyridine come from?
- In Carell's mechanism, the self-assembly of the purine bases with phosphate and ribose to form an RNA nucleotide.

Note that not all of these steps need to be demonstrated; only 1 or 2 will suffice.

Step 5: Evolution of RNA to DNA due to mutations

This has not been demonstrated conclusively, although there is good Systems Thinking logic that can explain this process.

Systems Thinking may be a valuable tool in understanding how these as-yet undemonstrated steps may have occurred, and indeed in guiding future experiments that attempt to reproduce them. An example is the Genesis Experiment.

6. The Genesis Experiment

The abiogenesis puzzle has many pieces, but most of them have been identified and validated experimentally, albeit individually. One remaining uber-experiment would integrate the various steps by starting with the raw materials thought to be present on the primordial earth, subjecting them to conditions that were thought to prevail, waiting, and detecting a virus-like entity in the condensate. This would follow the Miller-Urey protocol but also subject the components to thermal and moisture cycling, UV radiation, cycles of day and night, precipitation, pH cycling, interfaces between land-water, air-water, etc., hot springs, hot vents, and concentration gradients, and it would necessarily run for a long time; perhaps years. Inasmuch as the experiment would attempt to compress the events of ~1 billion years into ~1 year, some means (perhaps thermal cycling) would need to be used to accelerate reactions and events. Seeking out the feedback loops, hierarchical structures, and self-organization that are taught by Systems Thinking may help guide this experiment to successful completion, thus validating the abiogenesis hypothesis. The experiment might run like this:

1) Set up an apparatus similar to Miller-Urey's.
2) Start with a gas mixture comprising species that were thought to be present on the primitive earth, specifically H_2S, CO_2, NO_x, NH_3, CH_2, CH_4, H_2, P, H_20, HCN, SO_2, N_2, OCS (carbonyl sulfide).
3) Add as condensation substrates: montmorillonite clay, iron, nickel.
4) Ensure the existence of liquid-solid, liquid-gas, solid-gas, and solid-solid interfaces that are both constant and periodic (like ocean waves and tides, which alternately cover and uncover the beach).
5) Provide both protected and unprotected (exposed) physical locations.
6) Cycle temperature, moisture, pH, and light-and-dark, in various combinations and with varying periodicity.
7) Subject the gases to periodic electric discharges, UV radiation, and cosmic rays.
8) Let the experiment run for many months; perhaps even years.
9) Sample the condensate products regularly.
10) Iteratively identify by trial-and-error the specific conditions of temperature, moisture, periodicity, etc. that yield the most complex products and continuously tune the experiment to those conditions in a feedback loop.

Looking at the pre-biotic chemicals as components of a system that includes the land, the atmosphere, energy sources, weather, and other physical-chemical elements; understanding the feedback loops that were in play; recognizing that living things, components of living things, DNA, and everything in between are hierarchical; and appreciating the underlying forces that cause self-organization and emergence all contribute to an understanding and acceptance of abiogenesis as the explanation for life on earth.

REFERENCES

[1] Monat, J.; Amissah, M.; Gannon, T. Practical Applications of Systems Thinking to Business. *Systems* 2020, 8, 14.

[2] Monat, J.; Gannon, T. What Is Systems Thinking? A Review of Selected Literature Plus Recommendations. *Am. J. of Systems Science 2015,* 4, 2.

[3] Monat, J. P.; Gannon, T. *Using Systems Thinking to Solve Real-World Problems*, College Publications, Rickmansworth, England, U. K., 2017, 2.

[4] Camazine, S.; Deneubourg, J. L.; Franks, N.; Sneyd, J.; Theraula, G.; Bonabeau, E. *Self-Organization in Biological Systems,* Princeton University Press, Princeton, NJ, USA, 2001, p. 8.

[5] Kosikova, T.; Hassan, N.; Cordes, D.; Slawin, A.; Philp, D. Orthogonal Recognition Processes Drive the Assembly and Replication of a [2]Rotaxane. *J. Amer. Chem. Soc.* 2017, 137, 16074, https://doi.org/10.1021/jacs.5b09738.

[6] Dieckmann, A.; Beniken, S.; Lorenz, C.; Doltsinis, N.; von Kiedrowski, G. Unravelling a Fulvene Based Replicator: Experiment and Theory in Interplay. *Journal of Systems Chemistry*. 2010, 1, 10. http://www.jsystchem.com/content/1/1/10.

[7] Liu, Y.; Sumpter, D. Spontaneous Emergence of Self-Replication in Chemical Reaction Systems. *arXivLabs*. 2018, Cornell University, arXiv:1801.05872v2.

[8] Liu, B.; Pappas, C.; Ottelé, J.; Schaeffer, G.; Jurissek, C.; Pieters, P.; Altay, M.; Marić, I.; Stuart, M.; Otto, S. Spontaneous Emergence of Self-Replicating Molecules Containing Nucleobases and Amino Acids. *Journal of the American Chemical Society* 2020, 142, 4184-4192, DOI: 10.1021/jacs.9b10796.

[9] Clixby, G.; Twyman, L. Self-Replicating Systems. *Org. Biomol. Chem*. 2016, 14, 4170, DOI: 10.1039/c6ob00280c, www.rsc.org/obc.

[10] Szostak N.; Wasik S.; Blazewicz, J. Hypercycle. *PLoS Comput Biol* 2016, *12,* e1004853. doi:10.1371/journal.pcbi.1004853.

[11] Vaidya N.; Manapat, M. L.; Chen, I. A.; Xulvi-Brunet, R.; Hayden, E. J.; Lehman, N. Spontaneous Network Formation Among Cooperative RNA Replicators. *Nature* 2012, *491*, 72–7.

[12] Pross, A. Toward a General Theory of Evolution: Extending Darwinian Theory to Inanimate Matter. *ACS Nano* 2018, 12, 9750–9762; https://doi.org/10.1021/acsnano.8b05821.

[13] Monaco, R.; Montozon, F. (2006). Self-Organization, Autocatalysis and Models of the Origin of Life. Research Gate. 2005, https://www.researchgate.net/publication/228616096, accessed 9/25/2020.

[14] Wood, B. *Human Evolution*, Oxford University Press, Oxford, England, U.K., 2005, p 16.

[15] New, M.; Pohorille, A. An Inherited Efficiencies Model of Non-Genomic Evolution. *Simul. Pr. Theory* 2000, 8, 99-108.

[16] Crick, F. *Life Itself-Its Origin and Nature*, Simon and Schuster; New York, NY, USA, 1981, p 49.

[17] Emmeche, C.; Aspects of Complexity in Life and Science. *Philosophica.* 1997, 59, 1997, 41-68.

[18] Yeong, F. M. The Complexity of Life: Can Life be Simply Defined? *Journal of Biomolecular Structure and Dynamics* 2012, *29*, 617-618, DOI: 10.1080/073911012010525005.

[19] von Neumann, J. *Theory of Self-Reproducing Automata*, edited and completed by A. W. Burks. University of Illinois Press, Urbana, IL, USA, 1966.

[20] Bryson, W., *A Short History of Nearly Everything*, Broadway Books, New York, NY, USA, 2004, p. 185.

[21] DNA Learning Center. RNA Was the First Genetic Molecule. *DNA From the Beginning*. Cold Springs Harbor Laboratory. http://www.dnaftb.org/26/#:~:text=It%20now%20seems%20certain%20that, is%20easily%20damaged%20by%20enzymes, accessed 2 October 2020.

[22] Parker, N.; Schneegurt, M.; Thi Tu, A.; Forster, B. M.; Lister, P. *Microbiology*, OpenStax, Rice University, Houston, TX, USA, 2016, p 423.

[23] Hoyle, F.; Wickramasinghe, C. *Evolution From Space*, Touchstone/Simon & Schuster; New York, NY USA, 1981, pp. 23-24.

[24] Meadows, D., *Thinking in Systems*, Chelsea Green, White River Junction, VT, 2008, p. 83.

[25] Krissansen-Totton, J.; Arnet, G.; Catling, D. Constraining the Climate and Ocean pH of the Early Earth with a Geological Carbon Cycle Model. *Proceedings of the National Academy of Sciences* 2018, *115*, 4105-4110; DOI: 10.1073/pnas.1721296115 e0bd1681.

[26] Oró, J. Mechanism of Synthesis of Adenine from Hydrogen Cyanide Under Possible Primitive Earth Conditions, *Nature* 1961, *191*, 1193-1194.

[27] Bernal J. D. *The Physical Basis of Life*. London: Routledge and Kegan Paul: London, England, 1951, p. 364.

[28] Shimoyama, A.; Blair, N.; Ponnamperuma, C. Synthesis of Amino Acids Under Primitive Earth Conditions in the Presence of Clay. In *Origin of Life*; Noda N. H., Ed., Center for Academic Publisher, Tokyo, Japan, 1978; pp. 95−99.

[29] Yuasa, S. Polymerization of Hydrogen Cyanide and Production of Amino Acids and Nucleic Acid Bases in the Presence of Clay Minerals –In Relation to Clay and the Origin of Life. *Nendo Kagaku* 1989, *29*, 89−96 (in Japanese).

[30] Hashizume, H. Role of Clay Minerals in Chemical Evolution and the Origins of Life. *Clay Minerals in Nature – Their Characterization, Modification and Application.* 2012. IntechOpen; http://dx.doi.org/10.5772/50172.

[31] Keller, M.; Turchyn, A.; Ralser, M. Non-enzymatic Glycolysis and Pentose Phosphate Pathway-like Reactions in a Plausible Archean Ocean. *Mol Syst Biol.* 2014, *10*, 725; DOI: 10.1002/msb.20145228.

[32] Todisco, M.; Tommaso, P.; Fraccia, T. P.; Smith, G. P.; Corno, A.; Bethge L.; Klussmann, S.; Paraboschi, E. M.; Asselta, R.; Colombo, D.; Zanchetta, G.; Clark, N. A.; Bellini, T. Nonenzymatic Polymerization into Long Linear RNA Templated by Liquid Crystal Self-Assembly, *ACS Nano* 2018, *12*, 9750–9762.

[33] Powner, M. W.; Gerland, B.; Sutherland, J. D. Synthesis of Activated Pyrimidine Ribonucleotides in Prebiotically Plausible Conditions, *Nature* 2009, *459*; doi:10.1038/nature08013.

[34] Orgel, L. E. Prebiotic Chemistry and the Origin of the RNA World. *Crit. Rev. Biochem.* 2004, 39, 99-123; doi: 10.1080/10409230490460765.

[35] Israel, B. New Study Brings Scientists Closer to the Origin of RNA. *Georgia Tech News Center*. 2013. http://www.news.gatech.edu/2013/12/23/new-study-brings-scientists-closer-origin-rna, accessed 10/2/2020.

[36] Chen, M.; Cafferty, B.; Mamajanov,I.; Gállego, I.; Khanam, J.; Krishnamurthy, R.; Hud, N. Spontaneous Prebiotic Formation of a β-- ‑ ribofuranoside that Self-Assembles with a Complementary Heterocycle. *J. Am. Chem. Soc*. 2014, 136, 5640–5646.

[37] Becker, S.; Thoma, I.; Deutsch, A.; Gehrke, T.; Mayer, P.; Zipse, H.; Carell, T. A High-yielding, Strictly Regioselective Prebiotic Purine Nucleoside Formation Pathway. *Science*. 2016, 352, 833-6; DOI: 10.1126/science.aad2808.

[38] Szostak, J. W. Systems Chemistry on Early Earth, *Nature* 2009, *459*, 172.

[39] Sanchez, R. A.; Ferris, J. P.; Orgel, L. E. Cyanoacetylene in Prebiotic Synthesis, *Science* 1966, *154*, 784–785.

[40] Thaddeus, P. The Prebiotic Molecules Observed in the Interstellar Gas. *Phil. Trans. R. Soc. B* 2006, *361*, 1681–1687.

[41] Lincoln, T.; Joyce, G. Self-Sustained Replication of an RNA Enzyme. *Science*. 2009, 323, 1229–1232; DOI:10.1126/science.1167856.

[42] Robertson, M. P.; Joyce, G. F. Highly-Efficient Self-Replicating RNA Enzymes. *Chem Biol*. 2014, *21*, 238–245; doi:10.1016/j.chembiol.2013.12.004.

[43] Cojocaru, R.; Unrau, P. Origin of life: Transitioning to DNA genomes in an RNA World. *Insight.* 2017, eLife 2017; 6: e32330 DOI: 10.7554/eLife.32330.

[44] Lazcano A,; Fastag, J.; Gariglio, P.; Ramírez, C.; Oró, J. The Evolutionary Transition from RNA to DNA in Early Cells. *Journal of Molecular Evolution.* 1988, 27, 283–290.

[45] Meselson, M.; Stahl, F. The Replication of DNA in Escherichia coli. *PNAS*. 1958, 44, 671–82. DOI: 10.1073/pnas.44.7.671. PMC 528642. PMID 16590258.

[46] Kishimoto, T. Entry into Mitosis: a Solution to the Decades-long Enigma of MPF. *Chromosoma*. 2015. 124, 417–428; DOI 10.1007/s00412-015-0508-y.

[47] Lindquist, A.; Rodriguez-Bravo, V.; Medema, R. The Decision to Enter Mitosis: Feedback and Redundancy in the Mitotic Entry Network. *J. Cell. Biol*. 2009, 185, 193-202.

[48] Nishitani, H.; Lygerou, Z.; Control of DNA Replication Licensing in a Cell Cycle. *Genes to Cells* 2002, *7*, 523-534.

[49] Mullis, K.; Faloona, F.; Scharf, S.; Saiki, R.; Horn, G.; Erlich, H. Specific Enzymatic Amplification of DNA in Vitro: The Polymerase Chain Reaction. *Cold Spring Harbor Symposia on Quantitative Biology* 1986, 51, 263–273. DOI: 10.1101/sqb.1986.051.01.032. PMID 3472723.

[50] Moelling, K.; Broecker, F. Viruses and Evolution – Viruses First? A Personal Perspective. *Mol. Biol.* 2019, 39, 99–123, DOI.org/10.3389/fmicb.2019.00523.

[51] Khan Academy. Evidence for Evolution. https://www.khanacademy.org/science/high-school-biology/hs-evolution/hs-evidence-of-evolution/v/evidence-for-evolution, accessed 2 October 2020.

[52] Tamura, K.; Subramanian, S.; Kumar, S. Temporal Patterns of Fruit Fly (Drosophila) Evolution Revealed by Mutation Clocks, *Mol. Biol. Evol*. 2004, *21*, 36–44; DOI: 10.1093/molbev/msg236.

[53] Crick, F. *Life Itself-Its Origin and Nature*, Simon and Schuster; New York, NY, USA, 1981, pp. 171-175.

[54] Deamer, D.; Singaram, S.; Rajamani, S.; Kompanichenko, V.; Guggenheim, S. Self-Assembly Processes in the Prebiotic Environment. *Philos Trans R Soc Lond B Biol Sci.* 2006, 361, 1809-18; DOI: 10.1098/rstb.2006.1905.

[55] Fox, S.; Harada, K. Thermal Copolymerization of Amino Acids to a Product Resembling Protein. *Science.* 1958, 128, 1214; DOI: 10.1126/science.128.3333.1214.

[56] Rohlfing, D. L.; McAlhaney, W. W. The Thermal Polymerization of Amino Acids in the Presence of Sand, *Biosystems,* 1976, *8*, 139-145; https://doi.org/10.1016/0303-2647(76)90016-2.

[57] Leman, L.; Orgel, L.; Ghadiri, M. Carbonyl Sulfide-Mediated Prebiotic Formation of Peptides. *Science.* 2004, 306, 283-6; DOI: 10.1126/science.1102722.